

Application No. 10/518,817  
Amendment Dated December 1, 2005  
Reply to Office Action of September 26, 2005

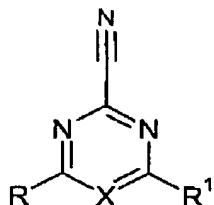
AstraZeneca Docket No. 100727-1P US

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

Claim 1. (currently amended) A method of inhibiting cathepsin S in a mammal comprising administering a compound of formula (I) to asid mammal



(I)

in which:

X is N- or CA where A is hydrogen, halogen,  $\text{CHR}^2\text{R}^3$ ,  $\text{OR}^2$ ,  $\text{NR}^2\text{R}^3$ , or  $\text{SR}^2$ ;

$\text{R}^2$  and  $\text{R}^3$  are independently hydrogen,  $\text{C}_{1-6}$  alkyl or  $\text{C}_{3-6}$  cycloalkyl both of which can optionally contain one or more O, S or  $\text{NR}^4$  groups where  $\text{R}^4$  is hydrogen or  $\text{C}_{1-6}$  alkyl, and can be optionally substituted by aryl, heteroaryl,  $\text{NR}^5\text{R}^6$  where  $\text{R}^5$  and  $\text{R}^6$  together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S,  $\text{NR}^4$ , or R2 and R3 together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S,  $\text{NR}^4$  group, or R2 and R3 are aryl or heteroaryl groups, both aryl and heteroaryl groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy,  $\text{CONR}^7\text{R}^8$ ,  $\text{SO}_2\text{NR}^7\text{R}^8$ ,  $\text{SO}_2\text{R}^4$ , trifluoromethyl,  $\text{NHSO}_2\text{R}^4$ ,  $\text{NHCOR}^4$ , ethylenedioxy, methylenedioxy,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{NR}^7\text{R}^8$  or  $\text{SR}^7$  where  $\text{R}^7$  and  $\text{R}^8$  are independently hydrogen or  $\text{C}_{1-6}$  alkyl;

R and  $\text{R}'$  are independently a group  $\text{Y}(\text{CH}_2)\text{pR}^9$  where p is 0, 1, 2 or 3 and Y is O or  $\text{NR}^{10}$  where  $\text{R}^{10}$  is hydrogen,  $\text{C}_{1-6}$  alkyl or  $\text{C}_{3-6}$  cycloalkyl;

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and R<sup>9</sup> is hydrogen, C<sub>1-6</sub> alkyl which can optionally contain one or more O, S or NR<sup>4</sup> groups where R<sup>4</sup> is hydrogen or C<sub>1-6</sub> alkyl, or a 3 to 7-membered saturated ring optionally containing a carbonyl group, one or more O, S or N atoms, or an aryl or heteroaryl group containing one to four heteroatoms selected from O, S or N, the saturated ring, aryl and heteroaryl groups all being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>4</sup>, trifluoromethyl, NSO<sub>2</sub>R<sup>4</sup>, NHCOR<sup>4</sup>, ethylenedioxy, methylenedioxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, SR<sup>5</sup> or NR<sup>11</sup>R<sup>12</sup> where R<sup>11</sup> and R<sup>12</sup> are independently hydrogen, C<sub>1-6</sub> alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR<sup>4</sup> group; or R/R<sup>1</sup> is a group NR<sup>10</sup>(CHR<sup>10</sup>) CONR<sup>2</sup>R<sup>3</sup> or NR<sup>10</sup>(CH<sub>2</sub>)<sub>q</sub>CONR<sup>2</sup>R<sup>3</sup> where q is 1, 2 or 3; or R/R<sup>1</sup> is a group NR<sup>13</sup>R<sup>14</sup> where R<sup>13</sup> and R<sup>14</sup> together with the nitrogen atom to which they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by C<sub>1-6</sub> alkyl, amino, hydroxy, CO<sub>2</sub>C<sub>1-6</sub> alkyl, halogen, NR<sup>5</sup>R<sup>6</sup>, NR<sup>7</sup>R<sup>8</sup>, C<sub>1-6</sub> alkylNR<sup>17</sup>R<sup>18</sup> where R<sup>17</sup> and R<sup>18</sup> are independently hydrogen or C<sub>1-6</sub> alkyl, CONR<sup>15</sup>R<sup>16</sup> where R<sup>15</sup> and R<sup>16</sup> are independently hydrogen or C<sub>1-6</sub> alkyl, or optionally substituted by aryl, phenoxy, COpheyl, or a heteroaryl group, the latter four groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>4</sup>, trifluoromethyl, NSO<sub>2</sub>R<sup>4</sup>, NHCOR<sup>4</sup>, ethylenedioxy, methylenedioxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, SR<sup>5</sup> or NR<sup>11</sup>R<sup>12</sup> where R<sup>11</sup> and R<sup>12</sup> are independently hydrogen, C<sub>1-6</sub> alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR<sup>4</sup> group;

~~and/or a pharmaceutically acceptable salt or solvates thereof, in the manufacture of a medicament for use in the inhibition of cathepsin S in a mammal such as man.~~

Claim 2. (currently amended) The method according to claim 1 in which X-A is CH, NHR<sup>2</sup>, or OR<sup>2</sup> wherein R<sup>2</sup> is hydrogen or C<sub>1-6</sub> alkyl.

Claim 3. (previously presented) The method according to claim 1 in which R is a group Y(CH<sub>2</sub>)<sub>p</sub>R<sup>7</sup> where p is 0 or 1 and Y is NR<sup>8</sup> wherein R<sup>8</sup> is hydrogen and R<sup>7</sup> is substituted phenyl.

Claim 4. (previously presented) The method according to claim 1 in which R<sup>1</sup> is a group NR<sup>13</sup>R<sup>14</sup> where R<sup>13</sup> and R<sup>14</sup> together with the nitrogen atom to which they are attached form a morpholine ring, piperidine or piperazine ring optionally substituted.

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**Claim 5. (previously presented)** The method according to claim 1 in which R<sup>1</sup> is a group NR<sup>9</sup>R<sup>10</sup> where R<sup>10</sup> is H or C<sub>1-6</sub> alkyl and R<sup>9</sup> is C<sub>1-6</sub> alkyl which can optionally contain one or more O, S or NR<sup>4</sup> groups where R<sup>4</sup> is hydrogen or C<sub>1-6</sub> alkyl.

**Claim 6.(currently amended)** The method according to claim 1 where the compound of formula (I) is selected from:

4-[(4-Chlorophenyl)amino]-6-(dimethylamine)-1,3,5-triazine-2-carbonitrile,  
4-Morpholin-4-yl-6-(4-phenoxy)peridin-1-yl)-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-(7-Azabicyclo[2.2.1]hept-7-yl)-6-[(4-chlorophenyl)amino]-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-pyrrolidin-1-yl-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-piperidin-1-yl-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(ethylamine)-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(3-hydroxypyrrolidin-1-yl)-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-[(2-piperidin-1-ylethyl)amino]-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(4-phenylpiperidin-1-yl)-1,3,5-triazine-2-carbonitrile,  
4-[(3-Chlorobenzyl)amino]-6-(dimethylamine)-1,3,5-triazine-2-carbonitrile,  
4-Morpholin-4-yl-6-[(4-morpholin-4-ylphenyl)amino]-1,3,5-triazine-2-carbonitrile,  
4-(2,3-Dihydro-1,4-benzodioxin-6-ylamine)-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-Morpholin-4-yl-6-(3-phenylpiperidin-1-yl)-1,3,5-triazine-2-carbonitrile,  
4-(1,4'-Bipiperidin-1'-yl)-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-[(1H-1imidazol-1-yl)piperidin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-[(4-(4-Chlorobenzoyl)piperidin-1-yl)-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-[(4-(5-Chloropyridin-2-yl)piperazin-1-yl)-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-Morpholin-4-yl-6-[(3-(2-oxopyrrolidin-1-yl)propyl)amino]-1,3,5-triazine-2-carbonitrile,  
1-(4-Cyano-6-morpholin-4-yl-1,3,5-triazin-2-yl)-N,N-diethylpiperidine-3-carboxamide,  
4-[(4-(2-Methoxyphenyl)piperazin-1-yl)-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
N-2-(4-Cyano-6-morpholin-4-yl-1,3,5-triazin-2-yl)-N-1-,N-1-bis[4-(4-cyano-6-morpholin-4-yl-1,3,5-triazin-2-yl)-N-isobutylglycyl]morpholin-3-yl]-N-2-isobutylglyciamide,  
4-Morpholin-4-yl-6-[(2-pyridin-3-ylethyl)amino]-1,3,5-triazine-2-carbonitrile,  
4-[(2-(2-Furyl)ethyl)amino]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(4-methylpiperazin-1-yl)-1,3,5-triazine-2-carbonitrile,  
4-Azetidin-1-yl-6-[(4-chlorophenyl)amino]-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,

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4-[(4-Methylcyclohexyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-(4-Chlorophenoxy)-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(dimethylamino)pyrimidine-2-carbonitrile,  
4-[(1-Methylpiperidin-4-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-(Cyclohexylamino)-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-pyrrolidin-1-ylpyrimidine-2-carbonitrile,  
4-[(6-Chloropyridin-3-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
1-{6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-L-prolinamide,  
4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]pyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(4-pyrrolidin-1-ylpiperidin-1-yl)pyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidine-2-carbonitrile,  
tert-Butyl 4-{6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl}piperazine-1-carboxylate,  
4-[(4-Chlorophenyl)amino]-6-(cyclopropylamino)pyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-piperazin-1-ylpyrimidine-2-carbonitrile,  
(2S)-N~2~-{6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-N~1~,N~1~-bis[4-(N-{6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-L-leucyl)morpholin-3-yl]-L-leucinamide,  
5-Chloro-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-5-methoxy-6-piperazin-1-ylpyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-5-methoxy-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-[(3S)-3-Aminopyrrolidin-1-yl]-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-{4-[3-(dimethylamino)propyl]piperazin-1-yl}-5-methoxypyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(dimethylamino)-5-methoxypyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-5-methoxy-6-(3-oxopiperazin-1-yl)pyrimidine-2-carbonitrile,  
1-{6-[(4-Chlorophenyl)amino]-2-cyano-5-methoxypyrimidin-4-yl}piperidine-3-carboxamide,  
4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-carbonitrile,  
5-Amino-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,and  
5-Amino-4-[(4-Chlorophenyl)amino]-6-(ethylamino)pyrimidine-2-carbonitrile,and  
and pharmaceutically acceptable salts thereof.

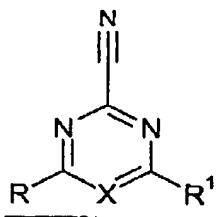
Claim 7. (cancelled)

Claim 8. (cancelled).

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Claim 9. (currently amended) A pharmaceutical composition which comprises a compound of formula (I):



(I)

in which:X is CA where A is hydrogen, halogen,  $\text{CHR}^2\text{R}^3$ ,  $\text{OR}^2$ ,  $\text{NR}^2\text{R}^3$ , or  $\text{SR}^2$ .

$\text{R}^2$  and  $\text{R}^3$  are independently hydrogen,  $\text{C}_{1-6}$  alkyl or  $\text{C}_{3-6}$  cycloalkyl both of which can optionally contain one or more O, S or  $\text{NR}^4$  groups where  $\text{R}^4$  is hydrogen or  $\text{C}_{1-6}$  alkyl, and can be optionally substituted by aryl, heteroaryl,  $\text{NR}^5\text{R}^6$  where  $\text{R}^5$  and  $\text{R}^6$  together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S,  $\text{NR}^4$ , or R2 and R3 together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S,  $\text{NR}^4$  group, or R2 and R3 are aryl or heteroaryl groups, both aryl and heteroaryl groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy,  $\text{CONR}^7\text{R}^8$ ,  $\text{SO}_2\text{NR}^7\text{R}^8$ ,  $\text{SO}_2\text{R}^4$ , trifluoromethyl,  $\text{NHSO}_2\text{R}^4$ ,  $\text{NHCOR}^4$ , ethylenedioxy, methylenedioxy,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{NR}^7\text{R}^8$  or  $\text{SR}^7$  where  $\text{R}^7$  and  $\text{R}^8$  are independently hydrogen or  $\text{C}_{1-6}$  alkyl;

$\text{R}$  and  $\text{R}'$  are independently a group  $\text{Y}(\text{CH}_2)\text{pR}^9$  where  $\text{p}$  is 0, 1, 2 or 3 and  $\text{Y}$  is O or  $\text{NR}^{10}$  where  $\text{R}^{10}$  is hydrogen,  $\text{C}_{1-6}$  alkyl or  $\text{C}_{3-6}$  cycloalkyl;

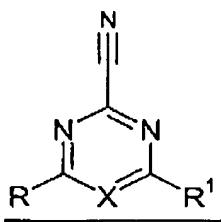
and  $\text{R}^9$  is hydrogen,  $\text{C}_{1-6}$  alkyl which can optionally contain one or more O, S or  $\text{NR}^4$  groups where  $\text{R}^4$  is hydrogen or  $\text{C}_{1-6}$  alkyl, or a 3 to 7-membered saturated ring optionally containing a carbonyl group, one or more O, S or N atoms, or an aryl or heteroaryl group containing one to four heteroatoms selected from O, S or N, the saturated ring, aryl and heteroaryl groups all being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy,  $\text{CONR}^7\text{R}^8$ ,  $\text{SO}_2\text{NR}^7\text{R}^8$ ,  $\text{SO}_2\text{R}^4$ , trifluoromethyl,  $\text{NHSO}_2\text{R}^4$ ,  $\text{NHCOR}^4$ , ethylenedioxy,

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methyleneedioxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, SR<sup>5</sup> or NR<sup>11</sup>R<sup>12</sup> where R<sup>11</sup> and R<sup>12</sup> are independently hydrogen, C<sub>1-6</sub>alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR<sup>4</sup> group;  
or R/R<sup>1</sup> is a group NR<sup>10</sup>(CHR<sup>10</sup>) CONR<sup>2</sup>R<sup>3</sup> or NR<sup>10</sup>(CH<sub>2</sub>)<sub>q</sub>CONR<sup>2</sup>R<sup>3</sup> where q is 1, 2 or 3;  
or R/R<sup>1</sup> is a group NR<sup>13</sup>R<sup>14</sup> where R<sup>13</sup> and R<sup>14</sup> together with the nitrogen atom to which they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by C<sub>1-6</sub>alkyl, amino, hydroxy, CO<sub>2</sub>C<sub>1-6</sub>alkyl, halogen, NR<sup>5</sup>R<sup>6</sup>, NR<sup>7</sup>R<sup>8</sup>, C<sub>1-6</sub>alkylNR<sup>17</sup>R<sup>18</sup> where R<sup>17</sup> and R<sup>18</sup> are independently hydrogen or C<sub>1-6</sub>alkyl, CONR<sup>15</sup>R<sup>16</sup> where R<sup>15</sup> and R<sup>16</sup> are independently hydrogen or C<sub>1-6</sub>alkyl, or optionally substituted by aryl, phenoxy, COpheyl, or a heteroaryl group, the latter four groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>4</sup>, trifluoromethyl, NHSO<sub>2</sub>R<sup>4</sup>, NHCOR<sup>4</sup>, ethylenedioxy, methylenedioxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, SR<sup>5</sup> or NR<sup>11</sup>R<sup>12</sup> where R<sup>11</sup> and R<sup>12</sup> are independently hydrogen, C<sub>1-6</sub>alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR<sup>4</sup> group, a compound of the formula (4) as defined in claim 7 or a pharmaceutically acceptable salt thereof;  
and a pharmaceutically acceptable diluent or carrier.

Claim 10. (currently amended) A method for producing inhibition of a cysteine-protease in a mammal, such as man, in need of such treatment, which comprises comprising:  
 -administering to said a mammal an effective amount of a compound of formula (I);



(I)

in which:

X is CA where A is hydrogen, halogen, CHR<sup>2</sup>R<sup>3</sup>, OR<sup>2</sup>, NR<sup>2</sup>R<sup>3</sup>, or SR<sup>2</sup>;

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R<sup>2</sup> and R<sup>3</sup> are independently hydrogen, C<sub>1-6</sub> alkyl or C<sub>3-6</sub> cycloalkyl both of which can optionally contain one or more O, S or NR<sup>4</sup> groups where R<sup>4</sup> is hydrogen or C<sub>1-6</sub> alkyl, and can be optionally substituted by aryl, heteroaryl, NR<sup>5</sup>R<sup>6</sup> where R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR<sup>4</sup> or R<sup>2</sup> and R<sup>3</sup> together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR<sup>4</sup> group, or R<sup>2</sup> and R<sup>3</sup> are aryl or heteroaryl groups, both aryl and heteroaryl groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>4</sup>, trifluoromethyl, NHSO<sub>2</sub>R<sup>4</sup>, NHCOR<sup>4</sup>, ethylenedioxy, methylenedioxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, NR<sup>7</sup>R<sup>8</sup> or SR<sup>7</sup> where R<sup>7</sup> and R<sup>8</sup> are independently hydrogen or C<sub>1-6</sub> alkyl;

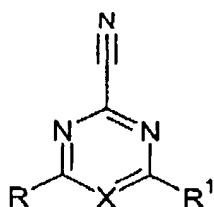
R and R<sup>1</sup> are independently a group Y(CH<sub>2</sub>)<sub>p</sub>R<sup>9</sup> where p is 0, 1, 2 or 3 and Y is O or NR<sup>10</sup> where R<sup>10</sup> is hydrogen, C<sub>1-6</sub> alkyl or C<sub>3-6</sub> cycloalkyl; and R<sup>9</sup> is hydrogen, C<sub>1-6</sub> alkyl which can optionally contain one or more O, S or NR<sup>4</sup> groups where R<sup>4</sup> is hydrogen or C<sub>1-6</sub> alkyl, or a 3 to 7-membered saturated ring optionally containing a carbonyl group, one or more O, S or N atoms, or an aryl or heteroaryl group containing one to four heteroatoms selected from O, S or N, the saturated ring, aryl and heteroaryl groups all being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>4</sup>, trifluoromethyl, NHSO<sub>2</sub>R<sup>4</sup>, NHCOR<sup>4</sup>, ethylenedioxy, methylenedioxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, SR<sup>5</sup> or NR<sup>11</sup>R<sup>12</sup> where R<sup>11</sup> and R<sup>12</sup> are independently hydrogen, C<sub>1-6</sub> alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR<sup>4</sup> group; or R/R<sup>1</sup> is a group NR<sup>10</sup>(CHR<sup>10</sup>) CONR<sup>2</sup>R<sup>3</sup> or NR<sup>10</sup>(CH<sub>2</sub>)<sub>q</sub>CONR<sup>2</sup>R<sup>3</sup> where q is 1, 2 or 3; or R/R<sup>1</sup> is a group NR<sup>13</sup>R<sup>14</sup> where R<sup>13</sup> and R<sup>14</sup> together with the nitrogen atom to which they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by C<sub>1-6</sub> alkyl, amino, hydroxy, CO<sub>2</sub>C<sub>1-6</sub> alkyl, halogen, NR<sup>5</sup>R<sup>6</sup>, NR<sup>7</sup>R<sup>8</sup>, C<sub>1-6</sub> alkylNR<sup>17</sup>R<sup>18</sup> where R<sup>17</sup> and R<sup>18</sup> are independently hydrogen or C<sub>1-6</sub> alkyl, CONR<sup>15</sup>R<sup>16</sup> where R<sup>15</sup> and R<sup>16</sup> are independently hydrogen or C<sub>1-6</sub> alkyl, or optionally substituted by aryl, phenoxy, C<sub>6</sub>phenyl, or a heteroaryl group, the latter four groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>4</sup>, trifluoromethyl, NHSO<sub>2</sub>R<sup>4</sup>, NHCOR<sup>4</sup>, ethylenedioxy, methylenedioxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, SR<sup>5</sup> or NR<sup>11</sup>R<sup>12</sup> where R<sup>11</sup> and R<sup>12</sup> are independently hydrogen, C<sub>1-6</sub> alkyl or together with the nitrogen atom to which they are attached form a 5-

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or 6-membered saturated ring optionally containing a further O, S or NR<sup>4</sup> group a compound of the present invention as defined in claim 7 or a pharmaceutically acceptable salt thereof.

**Claim 11. (new)** A method treating rheumatoid arthritis in a mammal comprising administering a compound of formula (I) to said mammal



(I)

in which:

X is CA where A is hydrogen, halogen, CHR<sup>2</sup>R<sup>3</sup>, OR<sup>2</sup>, NR<sup>2</sup>R<sup>3</sup>, or SR<sup>2</sup>;

R<sup>2</sup> and R<sup>3</sup> are independently hydrogen, C<sub>1-6</sub> alkyl or C<sub>3-8</sub> cycloalkyl both of which can optionally contain one or more O, S or NR<sup>4</sup> groups where R<sup>4</sup> is hydrogen or C<sub>1-6</sub> alkyl, and can be optionally substituted by aryl, heteroaryl, NR<sup>5</sup>R<sup>8</sup> where R<sup>5</sup> and R<sup>8</sup> together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR<sup>4</sup>, or R<sup>2</sup> and R<sup>3</sup> together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR<sup>4</sup> group, or R<sup>2</sup> and R<sup>3</sup> are aryl or heteroaryl groups, both aryl and heteroaryl groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>4</sup>, trifluoromethyl, NSO<sub>2</sub>R<sup>4</sup>, NHCOR<sup>4</sup>, ethylenedioxy, methylenedioxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, NR<sup>7</sup>R<sup>8</sup> or SR<sup>7</sup> where R<sup>7</sup> and R<sup>8</sup> are independently hydrogen or C<sub>1-6</sub> alkyl;

R and R<sup>1</sup> are independently a group Y(CH<sub>2</sub>)pR<sup>9</sup> where p is 0, 1, 2 or 3 and Y is O or NR<sup>10</sup> where R<sup>10</sup> is hydrogen, C<sub>1-6</sub> alkyl or C<sub>3-8</sub> cycloalkyl; and R<sup>9</sup> is hydrogen, C<sub>1-6</sub> alkyl which can optionally contain one or more O, S or NR<sup>4</sup> groups where R<sup>4</sup> is hydrogen or C<sub>1-6</sub> alkyl, or a 3 to 7-membered saturated ring optionally containing a carbonyl group, one or more O, S or N atoms, or an aryl or heteroaryl group containing

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one to four heteroatoms selected from O, S or N, the saturated ring, aryl and heteroaryl groups all being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>4</sup>, trifluoromethyl, NHSO<sub>2</sub>R<sup>4</sup>, NHCOR<sup>4</sup>, ethylenedioxy, methylenedioxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, SR<sup>5</sup> or NR<sup>11</sup>R<sup>12</sup> where R<sup>11</sup> and R<sup>12</sup> are independently hydrogen, C<sub>1-6</sub>alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR<sup>4</sup> group; or R/R<sup>1</sup> is a group NR<sup>10</sup>(CHR<sup>10</sup>)CONR<sup>2</sup>R<sup>3</sup> or NR<sup>10</sup>(CH<sub>2</sub>)<sub>q</sub>CONR<sup>2</sup>R<sup>3</sup> where q is 1, 2 or 3; or R/R<sup>1</sup> is a group NR<sup>13</sup>R<sup>14</sup> where R<sup>13</sup> and R<sup>14</sup> together with the nitrogen atom to which they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by C<sub>1-6</sub>alkyl, amino, hydroxy, CO<sub>2</sub>C<sub>1-6</sub>alkyl, halogen, NR<sup>5</sup>R<sup>6</sup>, NR<sup>7</sup>R<sup>8</sup>, C<sub>1-6</sub>alkylNR<sup>17</sup>R<sup>18</sup> where R<sup>17</sup> and R<sup>18</sup> are independently hydrogen or C<sub>1-6</sub>alkyl, CONR<sup>15</sup>R<sup>16</sup> where R<sup>15</sup> and R<sup>16</sup> are independently hydrogen or C<sub>1-6</sub>alkyl, or optionally substituted by aryl, phenoxy, COpheyl, or a heteroaryl group, the latter four groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>4</sup>, trifluoromethyl, NHSO<sub>2</sub>R<sup>4</sup>, NHCOR<sup>4</sup>, ethylenedioxy, methylenedioxy, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, SR<sup>5</sup> or NR<sup>11</sup>R<sup>12</sup> where R<sup>11</sup> and R<sup>12</sup> are independently hydrogen, C<sub>1-6</sub>alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR<sup>4</sup> group; or a pharmaceutically acceptable salt.

Claim 12. (new) The method according to claim 11 in which A is H, NHR<sup>2</sup>, or OR<sup>2</sup> wherein R<sup>2</sup> is hydrogen or C<sub>1-6</sub>alkyl.

Claim 13. (new) The method according to claim 11 in which R is a group Y(CH<sub>2</sub>)<sub>p</sub>R<sup>7</sup> where p is 0 or 1 and Y is NR<sup>8</sup> wherein R<sup>8</sup> is hydrogen and R<sup>7</sup> is substituted phenyl.

Claim 14. (new) The method according to claim 11 in which R<sup>1</sup> is a group NR<sup>13</sup>R<sup>14</sup> where R<sup>13</sup> and R<sup>14</sup> together with the nitrogen atom to which they are attached form a morpholine ring, piperidine or piperazine ring optionally substituted.

Claim 15. (new) The method according to claim 11 in which R<sup>1</sup> is a group NR<sup>9</sup>R<sup>10</sup> where R<sup>10</sup> is H or C<sub>1-6</sub>alkyl and R<sup>9</sup> is C<sub>1-6</sub>alkyl which can optionally contain one or more O, S or NR<sup>4</sup> groups where R<sup>4</sup> is hydrogen or C<sub>1-6</sub>alkyl.

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**Claim 16.(new) The method according to claim 11 where the compound of formula (I) is selected from:**

4-[(4-Chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-[(4-Methylcyclohexyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-(4-Chlorophenoxy)-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(dimethylamino)pyrimidine-2-carbonitrile,  
4-[(1-Methylpiperidin-4-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-(Cyclohexylamino)-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-pyrrolidin-1-ylpyrimidine-2-carbonitrile,  
4-[(6-Chloropyridin-3-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
1-{6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-L-prolinamide,  
4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]pyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(4-pyrrolidin-1-ylpiperidin-1-yl)pyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidine-2-carbonitrile,  
tert-Butyl 4-{6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl}piperazine-1-carboxylate,  
4-[(4-Chlorophenyl)amino]-6-(cyclopropylamino)pyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-piperazin-1-ylpyrimidine-2-carbonitrile,  
(2S)-N~2--{6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-N~1~,N~1--bis[4-(N-{6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-L-leucyl)morpholin-3-yl]-L-leucinamide,  
5-Chloro-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-5-methoxy-6-piperazin-1-ylpyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-5-methoxy-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-[(3S)-3-Aminopyrrolidin-1-yl]-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-{4-[3-(dimethylamino)propyl]piperazin-1-yl}-5-methoxypyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(dimethylamino)-5-methoxypyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-5-methoxy-6-(3-oxopiperazin-1-yl)pyrimidine-2-carbonitrile,  
1-{6-[(4-Chlorophenyl)amino]-2-cyano-5-methoxypyrimidin-4-yl}piperidine-3-carboxamide,  
4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-carbonitrile,  
5-Amino-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile, and  
5-Amino-4-[(4-Chlorophenyl)amino]-6-(ethylamino)pyrimidine-2-carbonitrile.